Spinal neuroblastomas
Diagnosis, treatment, and prognosis

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Nine cases of neuroblastoma and one of ganglioneuroma are discussed, and the value of gas myelography emphasized. The authors point out that neuroblastomas may make themselves known by cord compression, and are especially likely to do so in infancy. In patients under 1 year old, recognition of cord compression may be extremely difficult, but appropriate treatment is often curative, and early diagnosis is therefore imperative. In older children the prognosis is much worse.

KEY WORDS: neuroblastoma • spinal cord compression • gas myelography • infancy • catecholamine secretion

INTRASPINAL tumors are rare in infancy and childhood, especially when compared with other tumors of the central nervous system. Among the intraspinal malignant tumors seen in very young patients, the neuroblastoma is the most common. It arises either primarily within the spinal canal, perhaps from posterior root ganglion primordia, or as an extension from a paraspinal mass arising in the sympathetic chain or suprarenal medulla. The benign counterpart of the neuroblastoma, the ganglioneuroma, may also occur in childhood.

Despite the malignant nature of neuroblastomas, long-term survival has occurred, possibly due to spontaneous regression or maturation to a benign non-progressive state. This favorable change is especially likely within the first year of life; in this period 2-year survival rates as high as 84% have been reported in large series of neuroblastomas in all sites. Unfortunately, recognition of cord compression in the infant can be very difficult, and only early diagnosis and surgical decompression will prevent permanent paraplegia or quadriplegia.

Analysis of Cases

Over 15 years (1958-1973), nine cases of neuroblastoma and one of ganglioneuroma were referred for neurosurgical assessment at the Adelaide Children's Hospital, South Australia. These 10 cases, with an eleventh case of an adult seen in the Royal Adelaide Hospital, are reported here.

Age and Sex

Seven patients were male and four female; this supports the male predominance observed by most writers. Seven were 3 years of age or less, also in accord with the ex-
experience of Russell and Rubinstein, who reported that about 70% of the patients were under 4 years. A similar age incidence was reported by Bodian and by Gross, et al. In the latter series, the youngest child was 4 hours old, and the eldest 16 years old. Elefant, et al., have reported an 8-day-old infant with a spinal neuroblastoma, and this infant had been followed until the age of 34 months. Rothner has reported the 10-month follow-up of an infant who had a spinal neuroblastoma removed at the age of 2 days; Williams also briefly mentions a patient born with paraplegia. In the present series, the youngest child came to our attention at the age of 8 weeks because of signs of respiratory failure; autopsy disclosed an extradural neuroblastoma compressing the upper cervical cord, causing tetraplegia.

Symptoms

The presenting symptoms of spinal neuroblastoma are variable, and sometimes bizarre. Usually two features are predominant: local pain and impaired cord function. Pain and irritability were evident in at least four of our cases. In one child with a cervical lesion, there was a well-marked torticollis, and in another, spinal curvature associated with striking plagiocephaly. Presumably both resulted from asymmetrical muscle spasm. Loss of motor and sphincter function was seen in eight cases, weakness of one or both legs in six, and of arms also in two. Urinary incontinence or frequency were occasional early signs in this series. Priapism was seen in one infant, but the significance was missed.

It must be stressed that progressive paraplegia can be very insidious in infancy. One 4-month-old infant was treated for obstinate constipation for some weeks before it became evident that she was paraplegic; 5 years later, she is well but still paraplegic.

Clinical symptoms referable to the systemic effects of the tumors were not prominent in this series. One 2-year-old child presented signs of well-marked ataxia, which was thought to be cerebellar. Although she did not show the chaotic eye movements (opsoclonus) emphasized by Solomon and Chutorian as a sign of an occult neuroblastoma, it does seem likely that this ataxia was indeed an example of cerebellar disease. Later this child also developed cord compression, and the signs of spinal and cerebellar disorder merged. Interestingly enough, the well-known case reported by Cushing and Wolbach passed through a similar stage of cerebellar ataxia which was vividly described by Foster Kennedy, although the significance was, of course, not then evident.

Chronic diarrhea has been reported as a manifestation of excessive catecholamine secretion. It was not encountered in our cases. One older boy did show nonspecific ill health, profuse nocturnal sweating, and failure to grow; these may have been general effects of his large thoracic ganglioneuroblastoma, which produced catecholamines in substantial quantities. This same boy was also one of two who had no clinical evidence of spinal involvement; the other, a girl with a large ganglioneuroma, was seen after a chance chest radiograph had disclosed an intrathoracic mass. These children are included in the series, however, because the proximity of their tumors to the spinal canal aroused concern; myelography was performed, and in the first boy did indeed reveal impending cord compression, which had not been suspected on clinical grounds.

Our only adult patient had symptoms referable to hypersecretion of noradrenaline. This case is so remarkable as to demand a brief report. The patient, a 36-year-old Australian man, complained of numbness, tingling, and poor circulation in the extremities. He exhibited arterial hypertension (200/110 mm Hg). This was sensitive to phentolamine; intravenous infusion at the rate of 1.0 mg/min over 5 minutes lowered the mean arterial pressure from 127 to 90 mm Hg. Oral administration of phenoxybenzamine (10 mg twice daily) also lowered the blood pressure, so that he then complained of the symptoms of postural hypotension. The urinary excretion of catecholamines was repeatedly above the upper limit of normal accepted in our laboratory. The numbness suggested a lesion of the cervical cord, and myelography showed an intramedullary cervical tumor. Laminectomy confirmed this diagnosis; the small biopsy taken had the histological appearance of an anaplastic tumor compatible with neuroblastoma. This diagnosis was supported by
bioassay of the excised tissue, which yielded noradrenaline and dopamine in amounts considered to be excessive (28.5 and 55 \( \mu g/gm \) respectively). Radiation was given, and the man remains well with no hypertensive symptoms 5 years later. Although the small quantity of tumor tissue examined does not justify absolute certainty of the diagnosis, we regard this as a rare, perhaps unique, case of intramedullary neuroblastoma secreting noradrenaline; the biochemical evidence for this diagnosis seems conclusive. The case is, however, so unusual that we report it with some hesitation.

**Hematology**

Hemoglobin values ranged from 8 to 15 gm/100 ml. No case showed immature blood cells in the peripheral smear at the time of diagnosis. However, one patient subsequently showed immature white cells in the blood smear, and bone marrow aspiration confirmed the suspected tumor infiltration. Bone marrow study showed infiltration by neuroblastoma, the only instance in our series. This case provided the first evidence of dissemination after an apparently successful operation for a thoracic and intraspinal tumor.

**Radiology**

*Plain Radiographs.* Plain x-ray films were available in nine cases. Three showed widening of the spinal canal; in one there was marked scalloping of the vertebral bodies as well as erosion of pedicles and expansion of an intravertebral foramen, all of which indicated an unsuspected intraspinal spread by a large thoracic tumor. In another case, similar findings confirmed intraspinal spread from a lumbar mass. Calcification of a para- spinal primary tumor was seen in two cases (Fig. 1 upper left). Calcification of intraspinal neuroblastoma was not seen, but has been recorded by others.\(^{16}\)

*Myelography.* Three children underwent myelography with Myodil, which clearly demonstrated the position of the tumor. Gas myelography was used in five cases, with filtered atmospheric air being injected by lumbar or cisternal puncture under general anesthesia. Tomography was usually done, although in children this aid is not essential. Myelography clearly demonstrated a complete block in one case; in three, gas outlined displacement of the subarachnoid space by extradural masses (Fig. 1 upper right), and in one (the child with a benign para-spinal ganglioneuroma) a normal subarachnoid space was visualized. Although these pictures are less easily interpreted than those made with radiopaque oils, their diagnostic value was perfectly adequate. It is our impression that the immediate effects of gas myelography are milder than those of Myodil, especially if the gas is allowed to escape after the investigation; however, this impression lacks objective confirmation. More certainly, one can expect that gas myelography will avoid the rare delayed effects of Myodil. Gas myelography has been used extensively in Scandinavia for many years, and its value in the diagnosis of spinal neuroblastoma was well shown by Prakash.\(^{19}\)

*Aortography.* In two cases, aortography was used to delineate the vascular anatomy of thoracic and lumbar neuroblastomas with intraspinal extension. The feeding arteries were well shown (Fig. 1 lower right), but no tumor circulation was seen. Moes and Berrington\(^{15}\) have shown that aortography will often reveal abnormal vasculature in paraspinal neuroblastomas. In one case, an inferior vena cavagram was also done, demonstrating partial caval blockade by tumor.

*Pyelography.* In three cases, intravenous pyelography demonstrated displacement of the upper portion of the ureter. This was attributed to the presence of an intraabdominal primary tumor, from which the intraspinal tumor had arisen by extension in continuity.

**Biochemistry**

Most patients with neuroblastoma excrete abnormal quantities of the metabolites of adrenaline and noradrenaline. In clinical practice, the urinary excretion of 3-methoxy-4-hydroxy mandelic acid (MHMA) is usually tested, although dopamine, homovanillic acid, and the metanephrines may also give valuable diagnostic information.\(^{9,21}\) Such estimations are useful both in the initial diagnosis and in the study of treated cases; in-
increasing postoperative urinary values suggest recurrence or metastasis.

Of our 11 cases, six showed MHMA excretions above the values considered normal in our laboratory. (Normal ranges vary with age, weight, and laboratory technique.) In three other cases, levels were normal; in two, excretions were not measured as the patients died before the possibility of neuroblastoma was considered.

Differential Diagnosis

In an infant presenting with paraparesis or paraplegia, many conditions need to be excluded, such as trauma to the spinal cord (including obstetrical trauma), poliomyelitis, various kinds of myelitis, and cerebral palsy or Werdnig-Hoffman disease. It is less obvious to the neurosurgeon that many non-neurological conditions (including scurvy, fracture of the clavicle, and torticollis) may be simulated by spinal tumors in infancy. Review of our cases shows that even very experienced pediatricians could be deceived by these tumors.

In older children, diagnosis was generally easier, although this was not so in one 2-year-old child who presented with cerebellar ataxia: the possibility of a neuroblastoma was entertained, but biochemical tests were normal, and the diagnosis was only established when the child developed compression of the spinal cord and cauda equina. In our
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one adult patient, the finding of arterial hypertension, together with poor peripheral circulation, led to biochemical tests; and the complaint of numbness in the hands, with certain reflex changes, justified a cervical myelogram.

Pathology

Site of Tumor. In three cases, the cervical cord alone was involved; in one, the tumor was cervicodorsal; in three, the tumors were thoracic; and in three others lumbar. The remaining case, described above, had a paraspinal thoracic ganglioneuroma without intraspinal extension.

Origin of Tumor. The origin of the tumor was not easily determined. The exposure provided by laminectomy may leave the surgeon in doubt as to whether the spinal tumor is primary, a hematogenous metastasis, or an extension in continuity from a paraspinal tumor. It seems likely that in four children the spinal tumors were of the latter type, sometimes, rather inappropriately, described as “dumb-bell” tumors. One was almost certainly a hematogenous metastasis. In another, the autopsy showed two masses, one in the spinal cord and one in the thoracic sympathetic chain; the pathologist believed these to be independent primary growths, but this interpretation is debatable. In three patients, including two long-term survivors, the operator thought that the neuroblastoma arose within the spinal canal. In the adult case the tumor presumably arose within the spinal cord.

Gross Morphology. These tumors formed fleshy, often well-circumscribed masses in the extradural space. Matson has stated that spinal neuroblastoma never penetrates the dura, but in our series this was seen in two patients, one of whom had an intradural extramedullary mass and had the longest survival period in our series. In our adult patient the tumor was wholly intramedullary.

Metastasis. One child had obvious metastases when the paraplegia became evident; another developed extensive bone-marrow infiltration.

Histopathology. Seven tumors were poorly differentiated neuroblastomas. Three were classed as ganglioneuroblastomas. In one of these, the intraspinal component appeared wholly benign and was labelled a ganglioneuroma; however, the thoracic component contained masses of partially differentiated neuroblastoma, and unhappily this tumor has since metastasized despite seemingly total surgical ablation. One case showed the uniform appearances of a benign ganglioneuroma.

Treatment

One infant and one child died before the diagnosis was established. The other nine underwent surgical treatment by laminectomy, thoracotomy, or both. When there was established cord compression, or the threat of it, decompressive laminectomy was usually carried out at once. It was not often possible to achieve a complete gross tumor removal; this was achieved only once in our series, in a child with an asymptomatic spinal extension of a large thoracic ganglioneuroblastoma. In seven other cases, decompressive laminectomy was performed, but the removal of the tumor was certainly incomplete, fragments being left around nerve roots or anteriorly to the spinal theca. In five of these cases, there was recovery of neural function, excellent and prolonged in two, partial but prolonged in another, excellent but brief in two. Only one infant, who had been paraplegic for some weeks before operation, failed to derive any benefit.

Ablation of the extraspinal component of a neuroblastoma may also be indicated. Thoracotomy permitted removal of the large extraspinal component of the ganglioneuroblastoma described and the single case of thoracic ganglioneuroma included in this series was also removed completely by thoracotomy. However, it is more difficult to excise such paraspinal tumors in the lumbar or thoracolumbar region, and in this series radiotherapy was the preferred method of treatment in such cases.

Recently, it has been our policy to supplement surgery with radiotherapy to the spinal area and to include in the field any paraspinal extension; this was done in six cases. Cyclophosphamide and vincristine were also given in varying combinations. The value of such combined therapy is discussed by Stella and co-workers, and by Evans. One of our earlier patients received no radio-
therapy and only vitamin B₁₂ as chemotherapy; he is very well after 8 years.

**Results**

Our single case of paraspinal ganglioneuroma has done well after extraspinal surgery. With such tumors, a good result should almost always be achieved, but it must be stressed that the diagnosis depends on careful histological examination. In one clinically comparable tumor, preliminary biopsy showed typical extensive well-differentiated ganglioneuroma, but more extensive examination showed large foci of neuroblastoma.

Of our 10 patients with neuroblastoma or ganglioneuroblastoma, three have died of their disease, two are alive but with suspicion of active metastasis, and four are apparently well, 8, 5, 5, and 4 years after decompressive laminectomy; one is still under treatment. With the remarkable exception of the adult patient, all of these encouraging long-term survivals occurred in patients who were very young when the disease became symptomatic; the oldest was 9 months. Thus, 75% of our patients seen in the first year of life have a 2-year cure rate; there are no 2-year survivors among the four children first seen at older ages. This experience is in accord with other studies. It is difficult to know whether the encouraging results in very young infants can be credited to radiotherapy and chemotherapy; as has been pointed out, our most felicitous case was treated only by subtotal ablation (which certainly reversed his neurological defect) and by vitamin B₁₂, whose value is extremely dubious.

Autopsy was done in the three fatal cases: two died of unrelieved or recurrent cervical cord compression, and only one from the effects of widespread metastatic dissemination.

**Discussion**

There is clearly a biological continuity between ganglioneuroma and neuroblastoma; although unequivocal examples of transformation are rare, it seems very probable that many, if not all, cases of successful treatment in infancy represent this process or something like it. This raises some most interesting speculations. We wish, however, only to emphasize some matters of great practical importance.

Neuroblastoma is an important cause of cord compression in infants and children; and in the very young, the prognosis for survival is remarkably good. If laminectomy and decompression are performed before irrevocable cord damage has been inflicted, then a real cure is quite possible. Unfortunately, it is precisely in this age group that diagnosis is hardest. We have reported three long-term survivors diagnosed in infancy, but only one is neurologically unscathed, while one is partially and the other totally paraplegic. Every effort, therefore, should be made to detect these tumors early and to perform decompressive laminectomy without delay.

Diagnosis begins with suspicion, and suspicion should be aroused by weakness of arm or leg, or by spinal irritability, sometimes evident as torticollis or scoliosis. Plain spinal radiographs and analysis of urinary catecholamines may be helpful. Myelography will be the conclusive investigation. We have stressed the value and simplicity of gas myelography, which in our hands has both demonstrated and excluded spinal tumors very well. Myodil will nevertheless be preferred by many.

Once the likelihood of neuroblastoma has been established, it is essential to search for evidence of disease in other areas. Cutaneous and hepatic metastases must be considered. A complete blood count must be performed; immature cells in the blood film may suggest marrow infiltration by tumor. Bone marrow aspiration is essential, regardless of the findings on peripheral blood examination. A chest radiograph and full radiographic skeletal survey are also mandatory, because of the frequency with which neuroblastoma metastasizes to the bone, particularly in children over 2 years old. When there is evidence of lower thoracic or lumbar cord compression, radiographic studies should be undertaken to search for tumor arising from the abdominal sympathetic chain. Intravenous pyelography may demonstrate displacement of the upper portion of the ureter, suggesting the presence of a tumor within the abdomen. These radiographic studies can now be comple-
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...mented by nuclear medical diagnostic procedures, notably skeletal scanning.

Treatment policies are still somewhat controversial. No one will contest the necessity of urgent decompressive laminectomy, and probably it will be agreed that surgical removal of intraspinal and paraspinal tumor tissue should be as radical as is consistent with safety. If extraspinal tumor is demonstrated by subsequent investigation, additional treatment by further surgical excision, irradiation, and chemotherapy may be indicated. There is, however, no general agreement as to the value of attempted surgical removal of a paraspinal mass (e.g., an intrabdominal primary growth) when excision is likely to be technically hazardous. Koop, et al., have long advocated subtotal excision of primary neuroblastoma, even in the presence of distant disease, but our experience has not confirmed the value of such an approach. If no extraspinal disease can be demonstrated, the decision to use postoperative radiotherapy and chemotherapy must be based on the operative findings at laminectomy, the histology of the tumor, and the age of the patient. Incomplete surgical removal of a malignant neuroblastoma should be followed by local irradiation and probably by chemotherapy, although the value of the latter is harder to establish. A similar approach is probably indicated even when total removal of a malignant extradural mass is achieved. By contrast, if the tumor is histologically a benign ganglioneuroma, no additional therapy is required if adequate surgical removal has been achieved; and even if this has not been possible, an expectant policy is probably correct. In very young infants, it may also be wise to withhold radiotherapy and chemotherapy, even when the tumor is histologically malignant, since the chance of spontaneous regression is high.

Prognosis in neuroblastoma seems to depend on the site of the tumor, the presence of distant metastases, and particularly the age of the patient. Histology is less helpful; while a pure ganglioneuroma is certainly a benign tumor, the behavior of ganglioneuroblastoma is unpredictable, and often very destructive. Undifferentiated neuroblastoma is also unpredictable in its course. Prognosis must therefore be guarded, except when the tumor is composed entirely of differentiated neurons. There is, however, ample evidence both in this series and in others that cure of neuroblastoma presenting in the first year of life is a real possibility, and an optimistic and energetic approach to treatment of this group of patients is therefore warranted. This potential for cure makes it all the more important that symptoms suggestive of cord compression are recognized early, and decompression performed before cord function is irreparably compromised. In older patients, the prognosis is very much worse. But even with these, as our single adult patient has shown, early diagnosis and appropriate therapy may sometimes be rewarded by an unexpected long-term survival.

When distant metastases, skeletal, visceral, or cutaneous, are demonstrated, the prognosis, of course, becomes much more grave. In older patients, this finding probably means that treatment of a spinal lesion should be confined to palliative procedures. In patients under 2 years, and especially those who are very young, there are convincing reports of regression of such metastases; although we have not ourselves observed this phenomenon, we recommend early and energetic surgical treatment of spinal compression in this age group, even in the presence of disseminated metastases.

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